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In Vitro Activity of Sulbactam-Durlobactam against *Acinetobacter baumannii* Clinical Isolates Collected in 2020 from China

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Abstract

Background: Sulbactam-durlobactam (SUL-DUR) is a β-lactam-β-lactamase inhibitor combination being developed for treatment of infections due to *Acinetobacter baumannii-calcoaceticus* complex (ABC) organisms, including multidrug-resistant and carbapenem-resistant strains, and has just completed a Phase 3 clinical trial to evaluate safety and efficacy. Although ABC infections are a global problem, in China, ABC cause a higher proportion of nosocomial infections and the frequency of reports describing carbapenem-resistant ABC are increasing. Here we present the *in vitro* activity of SUL-DUR against 150 *Acinetobacter baumannii* isolates collected in 2020 from geographically diverse areas of China.

Methods: 150 *A. baumannii* clinical isolates were collected during 2020 from Chinese study centers located in Chongqing, Hunan, Shandong, Shanxi and Yunnan. Isolates were selected based on geographic distribution and site of infection. Susceptibility testing was performed according to Clinical Laboratory Standards Institute (CLSI) guidelines. Data analysis was performed using CLSI breakpoint criteria where available.

Results: SUL-DUR was active against this collection of 150 Chinese *A. baumannii* isolates. The SUL-DUR MIC_{90} was 4 mg/L compared to >64 mg/L for SUL alone. Over 97% of isolates were inhibited at the SUL-DUR preliminary breakpoint of 4 mg/L. This level of activity was consistent across the five Chinese provinces and different infection sources with MIC_{90} values ranging from 2-4 mg/L. Only 26% of these isolates were susceptible to the carbapenems imipenem and meropenem. Additionally, these isolates displayed low levels of susceptibility to other antibiotics with 37%, 26%, and 37% susceptible to amikacin, levofloxacin and minocycline, respectively. Only colistin and tigecycline had potencies similar to SUL-DUR.

Conclusions: SUL-DUR demonstrated potent antibacterial activity against recent clinical isolates of *A. baumannii* collected in China. These data support the potential utility of SUL-DUR, if approved, for the treatment of antibiotic-resistant infections caused by *Acinetobacter baumannii-calcoaceticus* complex organisms from China.

Introduction

Sulbactam-durlobactam (SUL-DUR) is an antibiotic that has recently completed a Phase 3 clinical trial for the treatment of infections caused by *Acinetobacter baumannii-calcoaceticus* complex (ABC), including multidrug-resistant and carbapenem-resistant isolates[1]. The β-lactam sulbactam (SUL) is an inhibitor of a subset of class A β-lactamases that also has intrinsic antibacterial activity against ABC through inhibition of penicillin binding proteins PBP1 and PBP3[2]. However, degradation of SUL by a variety of β-lactamases present in most clinical ABC isolates limit its clinical use[3,4,5]. Durlobactam (DUR, formerly ETX2514) is a diazabicyclooctane (DBO) β-lactamase inhibitor with an expanded spectrum of activity compared to other DBO inhibitors, which includes coverage of a broad range of class A, C and D β-lactamases[3].

Although ABC are a global problem, they are particularly concerning in certain parts of the world such as China. ABC is the third most common nosocomial pathogen in China with carbapenem resistance rates rising from 45.6% in 2012 to >70% in 2017[6].

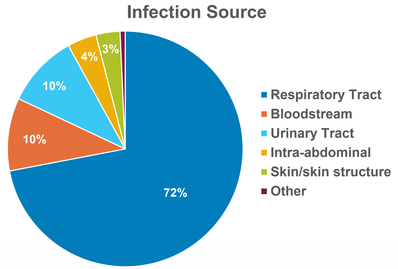
Here we present the *in vitro* activity of SUL-DUR against 150 *A. baumannii* clinical isolates collected in 2020 from geographically diverse areas of China.

Methods

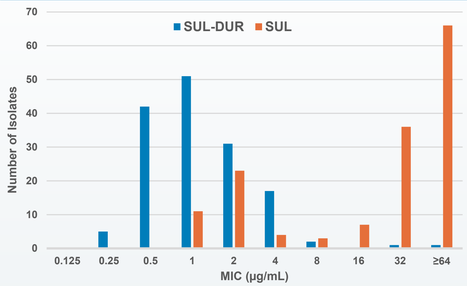
Broth microdilution susceptibility testing was conducted according to Clinical Laboratory Standards Institute (CLSI) guidelines[7]. SUL-DUR was tested by dilution of sulbactam in the presence of a fixed concentration of 4 µg/mL DUR. MIC testing was performed at IHMA China (Shanghai).

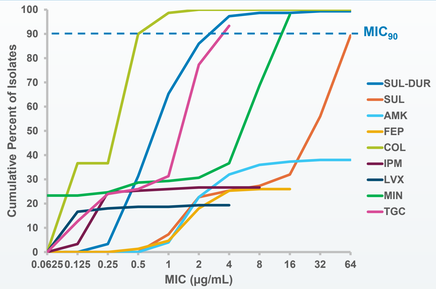
Study Design

The *in vitro* activity of SUL-DUR and comparator antibiotics was measured against 150 *A. baumannii* clinical isolates recovered in 2020 from five study centers in five different provinces in China.



Durlobactam Restores Sulbactam Activity against 150 *A. baumannii* Collected From China





Antimicrobial Agent	µg/mL			CLSI*		
	MIC_{50}	MIC_{90}	Range	% Susceptible	% Intermediate	% Resistant
Sulbactam-Durlobactam†	1	4	0.25 - >64	97.3	NA	2.7
Sulbactam	32	>64	1 - >64	NA	NA	NA
Imipenem	>8	>8	0.12 - >8	26.7	0	73.3
Cefepime	>16	>16	0.5 - >16	26	0	74
Amikacin	>64	>64	1 - >64	37.3	0.7	62
Levofloxacin	>4	>4	≤0.06 - >4	26	0	74
Colistin	0.5	0.5	≤0.25 - 2	NA	100	0.5
Minocycline	8	16	≤0.12 - >16	36.7	32	31.3
Tigecycline	2	4	0.12 - >4	NA	NA	NA

*Based on CLSI interpretative criteria[8]; NA, not available. †Sulbactam-durlobactam MICs were interpreted using preliminary breakpoints of ≤4 µg/mL susceptible and ≥8 µg/mL resistant[9].

In Vitro Activity of Sulbactam-Durlobactam is Stable Across Provinces Tested and Infection Sources

Province in China	N	Sulbactam-Durlobactam (µg/mL)			Percent with SUL-DUR MIC ≤ 4 µg/mL
		MIC_{50}	MIC_{90}	Range	
Chongqing	40	1	4	0.5 - 8	95
Hunan	20	1	4	0.5 - 32	95
Shandong	45	1	4	0.25 - >64	97.8
Shanxi	25	1	2	0.5 - 4	100
Yunnan	20	1	2	1 - 4	100
Infection Source					
Bloodstream	15	1	2	0.25 - 4	100
Intra-abdominal	6	NC*	NC	0.5 - 4	100
Respiratory Tract	108	1	4	0.25 - >64	96.3
Skin/skin structure	5	NC	NC	0.25 - 4	100
Urinary Tract	15	1	2	0.25 - 4	100
Other	1	NC	NC	1	100

*NC, not calculated for n<15

Characteristics of *A. baumannii* with Reduced Susceptibility to Sulbactam-Durlobactam

- 2.7% (4/150) of *A. baumannii* isolates had a sulbactam-durlobactam MIC ≥ 4 µg/mL, the preliminary breakpoint.
- All of these isolates were resistant to carbapenems and originated from three different Chinese provinces.

Province	Infection Source	MIC (µg/mL)								
		SUL-DUR	SUL	AMK	COL	IPM	FEP	LVX	MIN	TGC
Chongqing	Respiratory	8	64	16	≤0.25	>8	>16	>4	16	>4
Chongqing	Respiratory	8	64	32	0.5	>8	>16	>4	16	>4
Hunan	Respiratory	32	64	8	0.5	>8	>16	>4	0.5	1
Shandong	Respiratory	>64	>64	2	2	>8	4	2	>16	>4

Conclusions

- **Durlobactam restored sulbactam antibacterial activity against 150 *A. baumannii* clinical isolates collected in 2020 from five provinces in China with an MIC_{90} of 4 µg/mL.**
- **This set of isolates had high levels of resistance to other antibiotics, including carbapenems.**
- **97.3% of isolates were inhibited by ≤ 4 µg/mL of sulbactam-durlobactam, the preliminary breakpoint for sulbactam-durlobactam.**
- **Activity of sulbactam-durlobactam was consistent across isolates collected from different Chinese provinces, with MIC_{90} values ranging from 2 to 4 µg/mL.**
- **Sulbactam-durlobactam potency was also stable across all infection sources examined.**
- **These data support the development of sulbactam-durlobactam for the potential treatment of multidrug-resistant *A. baumannii-calcoaceticus* complex infections.**

References

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